1st EDITION

PRACTICAL TRAINING

HUMAN PAPILLOMAVIRUS

PRACTICAL CASES

MODULE 3.
PRIMARY PREVENTION OF HPV: VACCINES

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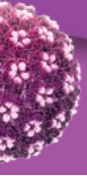
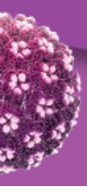
INTRODUCTION

The available vaccines against human papillomavirus (HPV; bivalent Cervarix®, and nonavalent Gardasil 9®), are very safe, efficacious, effective, and efficient at preventing HPV-dependent cancers of the cervix, vulva, vagina, penis, anus and oropharynx. The latest World Health Organization (WHO) position paper reaffirms this point[1]. The 2014 Spanish Cervical Cancer Screening Guidelines, published with the endorsement of eight Spanish Scientific Societies, explicitly provide strong support for HPV vaccination[2].



GOAL OF TREATMENT

The primary objective of this module is to provide updated scientific evidence that supports vaccination against HPV by clinicians.



1. CERVARIX®[3]

Cervarix® is a bivalent vaccine against HPV types 16/18, indicated for individuals at least 9 years old, for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal, and anal) and cervical and anal cancers caused by certain oncogenic types of HPV.

1.1. Vaccination Schedule

The schedule depends on the subject's age:

» From age 9 to 14 (inclusive): two doses, of 0.5 mL each. The second dose will be administered between 5 and 13 months after the first dose.

» From age 15: three doses, of 0.5 mL each, at 0, 1, and 6 months.

The minimum interval is 5 months between the first and second dose. If the second dose is administered after a shorter interval, a third dose should always be administered after another minimum interval has elapsed.

If the vaccination schedule needs to be adjusted, the second dose may be administered between 1 month and 2.5 months after the first dose, and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established.

Individuals who received a first dose of Cervarix® should complete the vaccination series with Cervarix®.

Cervarix® is not recommended for children under 9 years of age due to a lack of safety and immunogenicity data in this age group.

1.2. Administration

Cervarix® should be administered by intramuscular injection in the deltoid region. It should not be administered intravenously or intradermally under any circumstances. It may be administered concomitantly with a combined booster containing diphtheria (d), tetanus (T) and *pertussis* (acellular), with or without inactivated polio vaccine (IPV), (dTaP, dTaP/IPV vaccines), a combined Hepatitis A (inactivated) and Hepatitis B (rDNA) vaccine, or a Hepatitis B (rDNA) vaccine. These should not cause clinically relevant interference in the antibody response to the components of each vaccine.

There is no evidence that the use of hormonal contraceptives impacts the efficacy of Cervarix®.

There is limited immunogenicity data for asymptomatic subjects infected with human immunodeficiency virus (HIV). Otherwise, there are no data on the use of Cervarix® in subjects with an altered immune response, such as patients receiving immunosuppressant treatment.

As a precautionary measure, it is preferable to avoid Cervarix® during pregnancy. Women who are pregnant or trying to conceive are recommended to defer or interrupt vaccination until the end of the pregnancy.

In clinical trials, the effect of Cervarix® administration to nursing mothers has not been studied in their infants. Cervarix® should only be used during breastfeeding when the possible benefits outweigh the potential risks.

1.3. Safety

» **In clinical trials.** The most commonly observed adverse reaction following vaccine administration was pain at the injection site, which occurred following the administration of 78% of doses. The majority of these reactions were of mild to moderate severity and did not last long.

- Uncommon ε 1/1,000 to < 1/100:
  - Upper respiratory tract infection, dizziness, gastrointestinal disorders.

- Common ε 1/100 to < 1/10:
  - Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain.
  - Itching/pruritus, rash, urticaria at injection site.
  - Arthralgia, fatigue, fever ε38°C.

- Very common ε 1/10:
  - Headache.

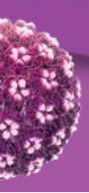
» **In post-marketing experience.** These occurrences are reported voluntarily, so it is not possible to reliably estimate their frequency:

- Blood and lymphatic system disorders: lymphadenopathy.
- Immune system disorders: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema.
- Nervous system disorders: syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements.

1.4. Efficacy

» Against high-grade cervical lesions associated with HPV-16/18, per protocol cohort, 95% CI:
- CIN2: 94.9% (87.7 - 98.4)
- CIN3: 91.7% (66.6 - 99.1)

» Against CIN2 positive for non-vaccine oncogenic types (cross-protection), per protocol cohort, 95% CI:
- HPV 31: 87.5 % (68.3– 96.1)
- HPV 33: 68.3 % (39.7– 84.4)
- HPV 39: 74.9% (22.3– 93.9)
- HPV 45: 81.9 % (17.0– 98.1)
- HPV 51: 54.4% (22.0– 74.2)



2. GARDASIL 9®[4]

Gardasil 9® is a nonavalent vaccine for HPV types 6/11/16/18/31/33/45/52/58. It is indicated for the active immunization of individuals at least 9 years old, against the following HPV-induced diseases:

» Precancerous lesions and cancers affecting the cervix, vulva, vagina, and anus caused by the HPV types targeted by the vaccine.

» Genital warts (Condyloma acuminata) caused by specific HPV types.

2.1. Vaccination Schedule

» For individuals from age 9 to 14 (inclusive) at the time of first injection:

- Gardasil 9® can be administered in a two-dose series for this age group. After the first dose, the second dose should be administered between 5 and 13 months later. If the second dose is administered before 5 months have elapsed following the first dose, a third dose should always be administered after another minimum interval has elapsed.

- Gardasil 9® can also be administered in a three-dose series (at 0, 2, and 6 months). The second dose should be administered at least one month after the first dose, and the third dose should be administered at least three months after the second dose. The three doses should be administered within a one-year period.

» For individuals age 15 and older at the time of first injection, Gardasil 9® should be administered in a three-dose series (at 0, 2, and 6 months). The second dose should be administered at least one month after the first dose, and the third dose should be administered at least three months after the second dose. The three doses should be administered within a one-year period.

Individuals who received a first dose of Gardasil 9® should complete the vaccination series with Gardasil 9®.

The need for a booster dose has not been established.

Subjects previously vaccinated with a three-dose series for the HPV types 6, 11, 16, and 18 in the tetravalent vaccine (Gardasil®) may receive three doses of Gardasil 9®.

The safety and efficacy of Gardasil 9® has not been established in children under 9 years of age.

2.2. Administration

The vaccine should be administered via intramuscular injection. The preferred site is the deltoid region of the upper arm or the anterolateral area of the thigh. Gardasil 9® should not be injected intravenously, subcutaneously, or intradermally.

As with all injectable vaccines, appropriate medical treatment and supervision must be readily available in the rare case of anaphylactic reaction following vaccine administration.

Individuals with an altered immune response, whether due to the use of a potent immunosuppressant therapy, genetic defect, human immunodeficiency virus (HIV) infection, or other causes, might not respond to the vaccine.

Gardasil 9® may be administered concomitantly with a combined booster for diphtheria (d), tetanus (T) and whooping cough/pertussis (acellular component) (aP) and/or (inactivated) polio vaccine (IPV), (dTaP, dT/IPV, dTaP/IPV vaccines). These should not significantly interfere with the antibody response to any of the components of either of the two vaccines.

60.2% of women aged 16 to 26 who received Gardasil 9® used hormonal contraceptives during the vaccination period of the clinical trials. The use of hormonal contraceptives did not appear to affect the immune response to Gardasil 9®.

Vaccination should be postponed until the end of pregnancy, but may be done while breastfeeding.

2.3. Safety

» **In clinical trials. Adverse reactions:**

- Common ε 1/100 to < 1/10:
  - Gastrointestinal symptoms: nausea.
  - Nervous system disorders: dizziness.
  - General disorders and administration site conditions: pyrexia, fatigue.
  - General disorders and administration site conditions: hematomas, itching.

- Very common ε 1/10:
  - Headache.
  - At the injection site: redness, pain, swelling.

» **In post-marketing experience:**

The following adverse reactions were reported voluntarily during use following the approval of Gardasil® and may also be observed in the post-marketing experience with Gardasil 9®. Both the Gardasil® and Gardasil 9® vaccines contain L1 proteins from HPV (of 4 of the same types of HPV). This means the post-marketing data from Gardasil® is relevant to Gardasil 9®. Because these occurrences were reported voluntarily by a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

- Infections or infestations: cellulitis at injection site.
- Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy.
- Immune system disorders: hypersensitivity reactions including anaphylactic/anaphylactoid reactions.
- Nervous system disorders: acute disseminated encephalomyelitis, Guillain-Barré syndrome, syncope occasionally accompanied by tonic-clonic movements.
- Gastrointestinal disorders: vomiting.
- Musculoskeletal and connective tissue disorders: arthralgia, myalgia.
- General disorders and administration site conditions: asthenia, chills, malaise.

2.4. Efficacy

» Against CIN2 associated with HPV 6, 11, 16, 18, 31, 33, 45, 52, 58, per protocol cohort, 95% CI: 96.9% (81.5– 99.8).

» Against CIN3, adenocarcinoma in situ (AIS) or cervical cancer associated with HPV 6, 11, 16, 18, 31, 33, 45, 52, 58, per protocol cohort, 95% CI: 100% (39.4– 100).

3. ADDITIONAL INFORMATION

- It should be noted that there is no upper age limit for administering the vaccine. There is no evidence that sexual activity limits its efficacy. The vaccine also protects against cervical cancer in all of its histological forms. Importantly, the vaccine can protect against adenocarcinoma, a form whose incidence has been increasing[5].

- When administering the vaccine following treatment, there is a strong, well-documented reduction in the risk of recurrence of intraepithelial lesions (Cervarix®: CIN1: 42.6%; CIN2: 88.2%; Gardasil®: CIN1: 48.1%; CIN2: 64.9%; genital warts: 63%)[6]. At this time, post-treatment vaccination must be considered a priority in conjunction with the therapeutic procedure.

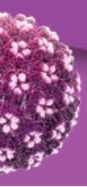
- Syncope (loss of consciousness) may occur after (or even before) any vaccination, especially in adolescents. This is sometimes associated with falls, as a psychogenic response to injection with the needle. Recovery may be accompanied by various neurological signs, such as transient visual impairment, paresthesia, and tonic-clonic movements of the extremities. Therefore, subjects should be carefully monitored for approximately 15 minutes after vaccination.

- Vaccination should be postponed in individuals who are suffering a severe febrile illness. Nevertheless, the presence of a mild infection, such as a mild upper respiratory tract infection or low fever, is not a contraindication for immunization.

- The vaccine is only indicated for prophylactic use and has no effect upon active HPV infections or on pre-existing clinical disease. The vaccine has not been demonstrated to have a therapeutic effect. Therefore, the vaccine is not indicated for the treatment of cervical cancer, vulvar, vaginal, or anal cancer, high-grade cervical, vulvar, vaginal, or anal lesions, or genital warts. It is also not indicated for preventing the progression of other lesions related to existing HPV.

- Vaccination is not a substitute for routine cervical screening. No vaccine is 100% effective, and it does not provide protection against all existing types of HPV or against pre-existing HPV infections at the time of vaccination. The importance of routine screening continues to be vital, and formulated recommendations should continue to be followed[2].

- The safety of the vaccine against HPV is demonstrated, with a highly beneficial benefit-to-risk ratio. The latest WHO position paper casts no doubts[7].



» There is no doubt about the efficiency and effectiveness of the vaccine against HPV, and prestigious publications have provided supportive evidence drawn from the highest level[8, 9, 10].

4. STATUS OF VACCINATION AGAINST HPV IN SPAIN

The vaccination rates recorded for Spain's public health (PH) programs as carried out by the Autonomous Communities are shown in Table 1[12]. It is encouraging news that the average coverage is close to 80%, clearly above the 70% level required to achieve efficiency and effectiveness[13].

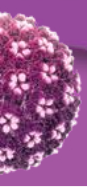
There are no official data from health care settings, but based on estimates from the medical divisions of the two vaccine manufacturers, coverage is very low. Among women not vaccinated through Public Health programs, only 1% have been vaccinated in health care settings[14]. The causes for this low coverage are identified[15]. Mainly, professionals' skepticism about efficacy and safety means they only provide *basic information* about the HPV vaccine. This falls short of providing a true, strong *recommendation* on vaccination. It is well-known that *recommendation* reinforces information, resulting in wider acceptance of the vaccine[16].

Table 1. Vaccine coverages for first and second doses of vaccine against HPV. Girls 13 – 14 years old. Year 2018.

AUTONOMOUS COMMUNITY	VACCINATION RATE
Andalusia	63.3
Aragon	88.3
Asturias	59.2
Balearic Islands	71.9
Canary Islands	85.3
Castile and León	90.9
Castilla La Mancha	75.6
Catalonia	82.4
Valencian Community	72.8
Extremadura	82.0
Galicia	75.3
Madrid	78.4
Murcia	83.7
Navarre	83.7
Basque Country	90.3
La Rioja	91.5
Ceuta	85.4
Melilla	85.0
MEAN	**77.5**

5. CONCLUSIONS. THE FUTURE OF VACCINATION AGAINST HPV

There have been many developments that can help eradicate cervical cancer in the medium term. Eradication has been highlighted as a plausible aim of the WHO[17] and has already been proposed as an attainable objective for some countries[18]. For example, primary prevention is facilitated by vaccination. Secondary prevention (early diagnosis) has now been facilitated by first-line HPV testing in programs redesigned for non-opportunistic population structures. These will work synergistically for disease eradication.



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